

Draft Guidance on Gefitinib

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Gefitinib

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 250 mg
Subjects: Healthy males, general population.
Additional Comments: Due to the risk of teratogenicity of gefitinib, the study should be conducted in healthy male volunteers.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 250 mg
Subjects: Healthy males, general population.
Additional Comments: See comments above

Analytes to measure (in appropriate biological fluid): Gefitinib in plasma

Bioequivalence based on (90% CI): Gefitinib

Waiver request of *in vivo* testing: N/A

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA)

In Vitro Comparative Nasogastric Tube Studies:

The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube. Conduct the following in vitro comparative testing using 8 French NG tube to compare the performance of the test product to that of the reference product to support NG tube administration.

NG tube preparation procedure: Prepare the NG tube studies using 12 units each of the test and the reference products for 0 and 15 minutes by the following procedure:

- 1) Prepare the dispersion by immersing one tablet (250 mg) in 4 to 8 ounces of water at pH > 7.0 with stirring for approximately 15 minutes and do not crush the tablet.
 - 2) Connect an oral syringe to the NG tube, transfer the drug dispersion into the oral syringe, and pass the dispersion through the NG tube into a collection container. Rinse the container with 4 to 8 ounces of water and immediately pass the rinse through the NG tube.
 - 3) Repeat the testing procedure described above with a fresh set of 12 units. However, after transferring the drug dispersion into the oral syringe in step (2), wait 15 minutes prior to passing the contents into the NG tube.
1. Comparative recovery testing: conduct comparative recovery studies to determine what percentage of the initial dose passes through a combination of oral syringe and NG tube. Follow the NG tube preparation procedure outlined above. Determine the percentage of gefitinib recovered at the NG tube exit relative to the initial dose for both the test and the reference products, using a validated analytical method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. If high variability is observed, the applicant may increase the number of units used for this test. Visually examine the tube and the syringe for any aggregation, adherence, clogging, etc.
 2. Risk assessment of administration conditions: NG tubes may be made with different materials (e.g., PVC, silicone, and polyurethane) which can impact the inner tube diameter. NG tubes are also available with different designs (e.g. number of ports and/or eyes; open or closed distal end) which can impact the flow of material through the tube. The applicant should consider the design of the various NG tubes that may be used for product administration, and test a representative selection (a minimum of 3) of tubes to ensure complete delivery of the drug product. Evaluation of testing conditions may be made on the basis of recovery study (testing procedure as above) and visual analysis and documented with photographs and videos.
 3. Standard operating procedure submission: submit standard operating procedures for the above in vitro NG tube testing. Include details about the tube and syringe used (e.g., material, brand, size, etc.), the type of water, the pH of water before and after dispersion of the tablets, flush volume used in the studies, holding positions of the tube, shaking method of the syringe, analytical site, testing dates, etc., for each of the studies. Submit individual data, mean values, standard deviations, and coefficient of variation (% CV) of the study in an Excel file. Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all observations and supporting photographs. Provide explanation if

additional pressure is needed to be applied during the testing to ensure complete recovery. Provide the pre-study validation report and within-study assay validation report. Conduct the above testing on unexpired test and reference batches.